THOUGHTS ON USING STEM CELLS TO TREAT SCHIZOPHRENIA AND OTHER FORMS OF PSYCHOSIS

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Abstract

Embryonic stem cell (ESC) research has shown to be of value in the potential treatment of neurological disease. There is evidence that at least some cases of schizophrenia have demonstrable areas of brain atrophy. There is thus the possibility of treating these cases using ESCs. If ESCs can be reliably controlled to differentiate into certain cell types, such as neurons and glia, it may be possible to re-grow brain tissue. Problem areas lie in the general ethics of ESC research, along with specific issues of research in psychiatric patients. There is also the practical issue of whether the new tissue will be accepted into the both the body and the organ.

Introduction

Before considering future uses of ESCs, the concepts and principles surrounding ESC research must be understood. A stem cell (SC) is "a precursor cell capable of differentiating into many different types of cells, which can form a powerful repair system for the body"[i]. Such cells are found in most multi-cellular organisms. SCs have two key features. One feature is that they are self renewing. Through mitotic cell division, a single mother cell forms two genetically identical daughter cells, meaning SCs have the potential to remain undifferentiated through many generations. The second feature is their potency by which, when differentiation is necessary, such as after the eight cell stage of a zygote, cell signaling resulting in modifications in gene expression can alter the size, shape, membrane potential, metabolic activity and responsiveness to signals, creating a specialized cell type. Within SCs, there are three different categories: somatic, fetal and embryonic; the latter will be discussed in this paper. Totipotent cells can differentiate to produce whole organisms, including extraembryonic tissue. ESCs are "SCs derived from the inner cell mass of an early stage embryo known as a blastocyst"[ii]. Such cells are pluripotent as they can differentiate into all three germ types: ectoderm, endoderm and mesoderm. The other SCs, especially somatic SCs, however, are partially differentiated and so can only become certain cell types. ESCs, therefore, are most useful in medicine.

The theoretical science surrounding ESC research is continually advancing as new developments are made. Within the trophoblast of a blastocyst is a hollow cavity called the blastocoel. Inside this is an inner cell mass containing around 40 SCs. To use these SCs, they are withdrawn and transported to a culture dish lined with a specialized medium containing growth factor. Here they continue to divide and multiply for months, with many factors being controlled such as the temperature and carbon dioxide / oxygen concentration, these being kept constant to simulate the mammalian body. The aim is to produce a SC line which is capable of reproducing indefinitely. A SC line is "a population of cells that can replicate themselves for long periods of time in vitro"[iii]. The challenge scientists face is preventing the cells from maturing until needed, and then ensuring the cells mature into the necessary cells. Scientists know that the factors involved in the signaling which causes differentiation are growth factors, genetics and chemical signals; however they currently do not understand the interaction of these factors.

Therefore, if it is discovered how to control the specialization of SCs, scientists would have the capability to produce all of the 220 different cell types in a human body giving the potential to treat hundreds of medical conditions in which cells die and need replacing. An example of the relevance of SCs to medicine is their usage for the past 30 years in bone marrow transplants, in which donor bone marrow is transplanted to leukemia patients so that the haematopoietic SCs may regenerate the patient's blood and immune system. The possibility of carrying out such transplants, but using ESCs which are instead pluripotent suggests even more possible treatments.

The importance of ESC research is well demonstrated through examples of current research promising to cure a number of common conditions using ESCs. One such example is research into SCs leading to advances in cancer therapies. Researchers believe that each tumour contains some SCs, which perpetuate the malignant tissue. This, it is thought, is the reason that anticancer drugs fail to permanently destroy cancerous growths. New anticancer drugs, developed alongside SC research, and targeting cancer SCs could be more successful[iv]. Another example by which SCs themselves could provide the cure is their possible use in the treatment of paralysis. The Geron trial, which will begin in the summer, will be the first in which a treatment based on ESCs will be tested on humans to investigate the efficacy and safety in patients with paralysis from the chest down. Another similar trial currently being planned is one in which ESCs will be used to grow retinal pigment epithelial cells to treat Acute Macular Degeneration (AMD), a disease in which these cells are destroyed causing blindness[v]. These three examples of the use of ESCs in medicine show their potential diversity. It also shows how ESC research is advancing to the extent that now, for the first time, clinical trials on humans are to take place. If these are successful, the first approved medical treatments based on ESCs could be licensed.

The focus of this paper is to use current research to propose the use of ESCs in the curative treatment of schizophrenia and related forms of psychosis. Schizophrenia is "a chronic, severe and disabling brain disease in which patients often suffer terrifying symptoms such as hearing internal voices or believing that other people are reading their minds, controlling their thoughts or plotting to harm them. These symptoms may leave them fearful and withdrawn. Their speech and behavior can be so disorganized that they may be incomprehensible or frightening to others"[vi]. It affects 1.1% of the world's population. Whilst the causes of schizophrenia are currently uncertain, research suggests that there may be potentially causative physical abnormalities in the brain. It is these which will be discussed here, and the possibility of reversing them using ESCs.

Discussion

It is currently possible to produce a SC line by which millions of undifferentiated cells can be created. It is hoped that further research will enable scientists to control how these cells specialize. Thus varying the necessary factors will modify gene expression in the way necessary to produce specific cells, such as erythrocytes or neurons. If this happens, since similar cells collect together to carry out a certain function by creating a tissue, these millions of undifferentiated cells could become a complete or partial tissue. Creation of such a tissue could enable tissue repair systems to work at a cellular level. These tissues could then be transplanted to replace damaged or dead tissue, similar to the creation of a new windpipe for a tuberculosis patient by scientists in Bristol in November 2008. This involved using strong chemicals and enzymes to destroy all the cells from a donor trachea, which was then repopulated with the patient's own cells derived from those lining her pre-existing windpipe and adult SCs removed from her bone marrow which were encouraged to grow into the cells that surround the windpipe[vii]. Although this tissue transplant did not involve ESCs it demonstrates the possibility of using new tissues to replace old tissues damaged by disease or injury.

It seems, therefore, that in order for ESCs to be effective in treating schizophrenia, there must be some loss or damage to tissue which can be replaced with a tissue transplant. Research into the causes of schizophrenia has suggested that there are differences between the brains of sufferers and non-sufferers, although there is still uncertainty whether these abnormalities are cause or effect of schizophrenia. Similarly there is doubt as to the reliability of these observations as they are not consistently present in sufferers nor absent in non-sufferers. Paul Thompson, Assistant Professor of Neurology at the UCLA School of Medicine, said regarding to a study of the brains of teenagers developing schizophrenia, "we were stunned to see a spreading wave of tissue loss that began in a small region of the brain. It moved across the brain like a forest fire, destroying more tissue as the disease progressed". Figure 1[viii] displays four images contrasting non-sufferers with sufferers of schizophrenia of both genders. The map is a composite map of a number of different subjects scanned using MRI, used to produce a 3-dimensional profile of the tissue loss that occurred in the teens. The red areas are areas of grey matter loss, which as shown here and in a number of different types of imaging, is particularly prevalent in the temporal and frontal brain regions that control attention, memory, hearing and motor function. Other abnormalities in the brains of sufferers include ventricular enlargement and decreased cerebral volume (average 3%)[ix]. It seems likely, therefore, that if this tissue death causes symptoms of schizophrenia, replacing this tissue may ameliorate the symptoms.

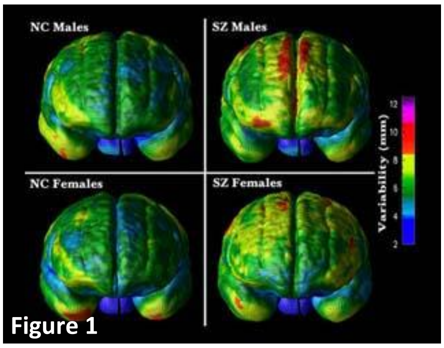

Figure 1

SCs could be the answer. Due to their plasticity, ESCs can become any type of cell including the three main types found in the brain: astrocytes, oligodendrocytes and neurons. Using the method discussed above, replacement brain tissue could be created and transplanted into the brains of sufferers. This tissue could be formed by differentiation of a SC line to form neurons surrounded by glial cells[1], which provide support and nutrition whilst sustaining homeostasis, creating myelin and partaking in signal transmission. It is indeed possible to produce neurons from ESCs, as research into treating Parkinson's has demonstrated[x], raising the possibility of similar treatment for other neurological diseases. In order for this to work, it must be possible for transplanted tissue to attach itself to the patient's brain and for neuropathways to form between the new tissue and the pre-existing tissue. In research investigating the possibility of reversing the progression of Huntington's chorea, fetal brain tissue was successfully transplanted into the brains of 5 sufferers, 3 of whom had shown an improvement in their symptoms a year later[xi]. It therefore seems that to create and transplant new brain tissue into the affected areas of brains of schizophrenic patients could reverse the progression of, or possibly even cure their symptoms. Alternatively, research from the University of Wisconsin suggests that, using neural SCs, it may be possible to regenerate adult differentiated glia and neurons[xii]. This bypasses the issue of differentiating pluripotent ESCs, whilst overcoming many ethical issues.

In order to understand the effectiveness of this treatment and thus whether it should take place, possible outcomes must be considered. The best possible outcome would be for the patient's body to accept the new brain tissue and for neuropathways to form between it and the rest of the brain such that it may become functional. It seems that in order for this to occur therapy may be necessary following the transplant for the patient to relearn lost skills, such as the ability to communicate effectively, make decisions and feel and express emotions. Whether this is possible or not is uncertain; however, when a baby is born they must learn such skills so, assuming the transplanted brain tissue resembles that of a new born baby, learning could occur in a similar way. Consequently, although the patient will not immediately recover, all positive symptoms should be relieved and disorganized or negative symptoms will begin to improve with time – as with the Huntington's chorea patients.

An alternative outcome could be the patient's body rejecting the transplanted tissue in graft-versus-host disease (GVHD), with symptoms including damage to liver, skin, mucosa, gastrointestinal tract and, according to newer research, the lungs and the immune system. This disease is staged from 1 to 4, where the prognosis becomes poorer nearer 4 in which fatal infection occurs due to damage to the immune system. In order to minimize the risk of developing GVHD, therapeutic cloning can be used to ensure the transplanted tissues are genetically virtually identical to the patient. In therapeutic cloning, the nucleus is removed from an unfertilized donor egg cell and replaced with a nucleus from one of the patient's own cells. A small amount of electricity is then used to simulate fertilization enabling this egg to begin dividing by mitosis to form an embryo from which ESCs can be removed. Their genes will be practically the same as those of the patient, reducing the risk of GVHD.

One important question is whether the treatment will be curative or provide symptomatic relief. This depends mainly on the cause of the schizophrenia. If the schizophrenia were genetic, treatment may only provide symptomatic relief as the underlying genetic problem would remain, causing continued loss of brain tissue. However, studies on identical twins, in which only one twin develops schizophrenia, make this cause less likely as, if entirely genetic, they would surely both develop the condition? More likely, therefore, the cause is an environmental insult such as illegal drug abuse or infection. In this case, if the insult is identified and removed, we could assume that the condition would not reoccur and thus the treatment could be curative.

This leads onto other possible uses of this treatment. One such use could be in other psychoses. There are a number of different forms of psychosis, such as delusional disorder and substance induced psychosis, in addition to schizophrenia, which can result from a number of different causes including brain tumours, drug abuse and severe clinical depression, however the relevant cause here is psychosis caused by brain damage. It seems that if

[1] Astrocytes and oligodendrocytes

psychosis is caused by brain damage, then if the brain damage can be reversed then the psychosis would end. Hence, a treatment similar to this discussed could be used to treat other forms of psychosis.

In order for ESC research to advance further, the ethics surrounding future developments must be considered. ESC research involves two conflicting moral principles. One such principle is that morally one should try to prevent and lessen suffering. The infinite possibilities of ESC research seem to satisfy this, since there is the potential to cure or relieve hundreds of different diseases causing suffering to patients and their families, and requiring long term support. However, another moral principle is that one should respect and value human life. ESC research, by destroying a potential life, could be said to violate this. Therefore, the decision must be weighed.

Firstly, this question must be answered: is an embryo a human life? At the stage when the ESCs are removed, the embryo is 4 or 5 days old – a "hollow microscopic ball of cells". What resemblance does this bear to human life? One common viewpoint held by individuals and many religions is that an embryo, by having the potential to become a human, should be given the same rights. According to Catholic teaching, life is created at the moment of conception, and thus removing the cells from the blastocyst could be classed as murder. An alternative viewpoint is that a bundle of unspecialized cells without any nervous system should be treated the same as any other collection of cells in the body, allowing ESC research. So with this question remaining unanswered, is it wrong to destroy an embryo? The majority of embryos used for research are sourced from IVF clinics as surplus embryos that would otherwise be destroyed. The 'parents', or perhaps donors would be a better description, have consented for the embryos to be used for research purposes. One could say that it is better to use them than allow them to be wasted. Otherwise, by giving so much respect to a collection of cells, the potential to cure lots of suffering is lost. This poses the question as to the difference between acts and omissions, as philosophers argue. Whilst the outcome, their being destroyed, may remain the same; is one option an act and the other an omission. The argument is that to remove the cells from the blastocyst is an act resulting in the death of the embryo, whereas to remove the embryo from the cold storage keeping it alive is an act of omission. However, one could suggest that actively removing the embryo from the cold storage is also an act resulting in its death, so are the two in fact identical except that by removing the cells there is the potential for benefit?

This potential must be defined by demonstrating the possible benefits of ESC research. Firstly, it should be noted that the use of ESCs poses fewer moral dilemmas than using fetal or somatic SCs as, not only are they more easily available, but the association with a 'life' is more tenuous. In this research, as discussed, lie potential cures or symptomatic relief for hundreds of different medical conditions, and consequential relief of suffering. Returning to the two conflicting moral principles: is failing to respect one embryo, questionably a 'life', in order to alleviate the suffering of thousands more, breaking any major moral principles? Putting this into context, approximately 1% of the world's population over the age of 18 suffers from this, arguably the worst, psychotic disorder. That is to say 24 million people in the world are known to suffer from schizophrenia[xiii]. If the treatment proposed here proved effective in only 10% of these, 2.4 million people would benefit and enormous savings in resources would be achieved. With regards to schizophrenia alone the benefits of ESC research sound convincing. Social and economic benefits should also be considered. The huge number of sufferers makes treatment expensive meaning resources could be made available for alternative uses if this ESC treatment becomes successful. Often, lack of resources means dangerous schizophrenics remain untreated leaving them a risk to society, as in the case of Ismail Dogan who killed a man due to his schizophrenia[xiv].

However, it must also be considered that there are potential disadvantages surrounding ESC research. Scientists may become desensitized to the sanctity of human life, which could lead to changes in science, governments and society. This could have an extremely detrimental effect. Human life should be treated with dignity so, whilst in this case it may 'only' be 4 day old collection of cells, the next stage would be closer. There is also the possibility of exploitation of women as egg donors. ESC research could be developed for commercial and profitable applications, comparable even to prostitution where a woman sells her body; in this case a woman would sell her ova. There are potential drawbacks to ESC research.

To prevent the misuse of such research and treatments, the law must be clear. After 2001 US law stated that scientists may not use government money to create new ESC lines so all publicly funded work is restricted to the 61 SC lines that already exist. On 9th March 2009, however, Barack Obama lifted this ban enabling the production of more stem cell lines[xv]. Privately funded ESC research, though, has never been forbidden and is mostly unregulated. In the UK there is more regulation. Any study involving SCs must be "licensed by the Human Fertilization and Embryology Authority, which can only occur if the creation or use of embryos is necessary and the work cannot be carried out any other way"[xvi]. The research can only be for limited purposes such as increasing knowledge about a serious disease. It is against the law in the UK to use an embryo after 14 days post conception when a nervous system begins to develop.

There are, in addition, specific ethical issues surrounding the use of ESCs in the treatment of schizophrenia. Most important is the question: is a person with such severe psychosis truly capable of consenting to a dangerous and invasive treatment? As already discussed, there would be no guarantees as to its success so harm could easily outweigh the benefits. This is pertinent in psychiatric disorders, in which preliminary animal testing is difficult. The law is very unclear surrounding the issue of ability to give consent, but generally "patient consent is the principle that you have to give express permission before any medical treatment can be carried out on you. Consent is needed, whatever the type of treatment, from a simple blood test to an organ donation"[xvii]. The giving of consent must be voluntary and informed. It would seem that a patient with such severe psychosis that they cannot formulate sentences or make decisions – two main symptoms of schizophrenia – is incapable of making the decision to give consent or understand the risks involved. This issue is currently being researched by the Department of Health[xviii].

Conclusion

In this paper, it has been suggested that new brain tissue could be cultured from ESCs to replace tissue that has died, thus offering symptomatic relief or cure for patients suffering from schizophrenia and other psychoses. The theory behind this has been discussed. However a number of problems have been identified. One practical problem is rejection. If the patient's body rejects the transplanted tissue they could develop GVHD which can be fatal. The best way to prevent this is by using therapeutic cloning as the SCs would then have virtually the same genetic makeup as the patient. Similarly, there may be a problem of the new tissue integrating into the pre-existing brain tissue. Another problem currently in discussion is that ESCs could have malignant potential, however recently a solution has been suggested that induced pluripotent stem (IPS) cells may be produced by reprogramming patients' skin cells into an ESC state[xix]. These IPS cells can also provide genetically matched cell lines to the patients whilst avoiding both ethical problems and the necessity for expensive technological equipment when working with ESCs.

A significant problem is the ethics surrounding the source of the ESCs. One way of overcoming this problem might be to encourage new mothers to store cord blood after they have given birth, so every baby will have a future supply of SCs. However, cord blood SCs are not as useful as ESCs as they are only hematopoietic rather than pluripotent. Therefore, they can only become a limited number of cells. Alternatively, SC lines with different genetic make-ups could be created so that whenever SCs are required they could be taken from the line most similar to the patient. Although this would involve destroying a certain number of embryos now, this would be finite. Perhaps the most promising alternative in the treatment of neurological disease is to use neural SCs from the patient themselves, though this would require two brain surgeries. Neural SCs removed from the developing human brain cortex, which have been shown to grow in the presence of leukemia inhibitory factor (LIF), migrate extensively around animal brains when injected, suggesting their potential to heal the human brain[xx]. Ethically, another problem arises with regard to consent by patients suffering from psychosis. The law in this field needs to be carefully defined. Other laws which must be carefully regulated are those surrounding the use of research, such as commercial uses; since otherwise ESC research may substitute business for humanitarian goals.

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